

CLAIMS

1. A method of stimulating or otherwise facilitating formation of colonies of mammalian pancreatic cells containing insulin-secreting cells, said method comprising culturing pancreatic cells in the presence of one or both of a bone morphogenetic protein (BMP) or a functional derivative, homologue, mimetic, analogue or agonist thereof or laminin-1 or laminin-1-containing extracellular matrix (ECM) or a functional derivative, homologue, mimetic, analogue or agonist thereof for a time and under conditions sufficient for colonies to form comprising insulin-secreting cells.

2. A method according to Claim 1 wherein the BMP molecule is a member of the TGF- β family.

3. A method according to Claim 2 wherein the BMP molecule is a heterodimer from two or more BMP molecules.

4. A method according to Claim 1 or 2 wherein laminin-1 is provided at a concentration of from about 1 $\mu\text{g/ml}$ to about 1000 $\mu\text{g/ml}$.

5. A method of stimulating or otherwise facilitating formation of colonies of mammalian pancreatic cells containing insulin-secreting cells, said method comprising culturing pancreatic cells in the presence of one or both of a bone morphogenetic protein (BMP) or a functional derivative, homologue, mimetic, analogue or agonist thereof for a time and under conditions sufficient for colonies to form comprising insulin-secreting cells.

6. A method of stimulating or otherwise facilitating formation of colonies of mammalian pancreatic cells containing insulin-secreting cells, said method comprising culturing pancreatic cells in the presence of laminin-1 or laminin-1-containing extracellular matrix (ECM) or a functional derivative, homologue, mimetic, analogue or agonist thereof for a time and under conditions sufficient for colonies to form comprising insulin-secreting

cells.

7. A method of stimulating or otherwise facilitating formation of colonies of mammalian pancreatic cells containing insulin-secreting cells, said method comprising culturing pancreatic cells in the presence of a bone morphogenetic protein (BMP) or a functional derivative, homologue, mimetic, analogue or agonist thereof or laminin-1 or laminin-1-containing extracellular matrix (ECM) or a functional derivative, homologue, mimetic, analogue or agonist thereof for a time and under conditions sufficient for colonies to form comprising insulin-secreting cells.

8. A method according to Claim 5 or 7 wherein the BMP molecule is a member of the TGF- β family.

9. A method according to Claim 8 wherein the BMP molecule is a heterodimer from two or more BMP molecules.

10. A method according to Claim 6 or 7 wherein laminin-1 is provided at a concentration of from about 1 $\mu\text{g/ml}$ to about 1000 $\mu\text{g/ml}$.

11. A method according to any one of Claims 1 to 10 wherein the pancreatic cells are pancreatic lineage embryonic stem cells.

12. A method of stimulating or otherwise facilitating formation of cystic epithelial colonies containing insulin-secreting cells, said method comprising culturing pancreatic cells in the presence of one or both of a BMP or a functional derivative or homologue, mimetic, analogue or agonist thereof and/or a laminin-1 or a laminin-1-containing ECM or a functional derivative, homologue, mimetic, analogue or agonist thereof for a time and under conditions sufficient for colonies to form comprising insulin-secreting cells.

13. A method according to Claim 12 wherein the BMP molecule is a member of

the TGF- β family/

14. A method according to Claim 13 wherein the BMP molecule is a heterodimer from two or more BMP molecules.

15. A method according to Claim 12 or 13 wherein laminin-1 is provided at a concentration of from about 1 $\mu\text{g/ml}$ to about 1000 $\mu\text{g/ml}$.

16. A method of stimulating or otherwise facilitating formation of cystic epithelial colonies containing insulin-secreting cells, said method comprising culturing pancreatic cells in the presence of a BMP or a functional derivative or homologue, mimetic, analogue or agonist thereof for a time and under conditions sufficient for colonies to form comprising insulin-secreting cells.

17. A method of stimulating or otherwise facilitating formation of cystic epithelial colonies containing insulin-secreting cells, said method comprising culturing pancreatic cells in the presence of laminin-1 or a laminin-1-containing ECM or a functional derivative, homologue, mimetic, analogue or agonist thereof for a time and under conditions sufficient for colonies to form comprising insulin-secreting cells.

18. A method of stimulating or otherwise facilitating formation of cystic epithelial colonies containing insulin-secreting cells, said method comprising culturing pancreatic cells in the presence of a BMP or a functional derivative or homologue, mimetic, analogue or agonist thereof and a laminin-1 or a laminin-1-containing ECM or a functional derivative, homologue, mimetic, analogue or agonist thereof for a time and under conditions sufficient for colonies to form comprising insulin-secreting cells.

19. ~~The~~ A method according to Claim 16 or 18 wherein the BMP molecule is a member of the TGF- β family.

20. ¹⁹A method according to Claim 19 wherein the BMP molecule is a

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heterodimer from two or more BMP molecules.

21. ~~A method according to Claim 17 or 18 wherein laminin-1 is provided at a concentration of from about 1 $\mu\text{g/ml}$ to about 1000 $\mu\text{g/ml}$.~~

22. A method of stimulating or otherwise facilitating formation of colonies containing insulin-secreting cells from pancreatic cells, said method comprising culturing pancreatic cells in the presence of a BMP and in the presence of an antagonist of Activin A or TGF- β 1.

23. A method for the treatment of a subject with type 1 diabetes or a related condition, said method comprising transplanting to said subject insulin-secreting cells produced following the *in vitro* culture of pancreatic cells in the presence of a BMP or a heterodimer formed from two or more BMPs or functional derivatives, homologues, mimetics, analogues or agonists thereof and optionally in the presence of laminin-1 or laminin-1-containing ECM or derivatives, homologues, mimetics, analogues or agonists thereof for at time and under conditions sufficient for colonies to form comprising insulin-secreting cells.

24. ~~A~~ method according to Claim 23 wherein the BMP is a member of the TGF- β family.

25. A method according to Claim 23 or 24 comprising culturing the cells in the presence of both a BMP and a laminin-1 or laminin-1-containing ECM.

26. A method for the treatment of a subject with type 1 diabetes or a related condition, said method comprising administering to said subject an effective amount of a BMP or a heterodimer formed from two or more BMPs or derivatives, homologues, mimetics, analogues and/or agonists thereof for a time and under conditions sufficient to facilitate insulin secretion in the pancreas of said subject.

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27. ^{the}~~A~~ method according to Claim 26 further comprising the administration of laminin-1 or laminin-1-containing ECM.

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28. ^{the}~~A~~ method for the treatment or prophylaxis of islet/ β cell hyperplasia adenoma or a related condition including pancreatic cancer, said method comprising administering to a subject an effective amount of an antagonist of a BMP for a time and under conditions sufficient to inhibit the formation or maintenance of insulin-producing β cells.

29. A method according to Claim 28 wherein the BMP antagonist is TGF- β or Activin A.

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